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THE INTERNATIONAL CONFERENCE FOR THE UNIFICATION OF THE FORMULÆ OF POTENT MEDICAMENTS.

(HELD AT BRUSSELS, SEPTEMBER 15–20, 1902.)

BY FREDERICK B. POWER.

A comparatively short period of time has elapsed since Dr. Frederick Hoffmann, of Berlin, contributed to this *Journal* (July–September, 1901) a very complete and interesting series of papers, entitled, "The International Pharmaceutical Congresses," which afford a comprehensive history of these organizations from the time of their inception—at the meeting of a French pharmaceutical society held at Strasburg, in 1864—to the Congress at Paris in 1900, which was the ninth of those inaugurated during the intervening years. In his presentation of the subject, Dr. Hoffmann has reviewed in a thorough and systematic manner the motives and guiding principles of these congresses and the scope of their deliberations. He has also clearly shown that, as hitherto constituted, they had failed to accomplish the purpose intended, and had been unproductive of any very definite or substantial results.[1]

In view of these facts, and, to a certain extent, as supplementary to the above-mentioned papers, it has seemed desirable that a somewhat complete account should be recorded of the Conference

[1] Compare also the report of Professor Remington on the International Pharmaceutical Congress held at Brussels in 1897 (*Proc. Amer. Phar. Assoc.*, 1898, pp. 103–108.)

[EDITOR'S NOTE.—A group photograph of the delegates to the International Conference was made to accompany this article, but the copies were delayed *en route* from England, and will be inserted in a later issue.]

recently held at Brussels, which was designated by the title forming the subject of this communication.

It will be observed, as the title implies, that this Conference was quite distinct in its character from the various pharmaceutical congresses that have preceded it, although it was a development of them. It was international not only in name, but in fact, as will be seen by the countries represented, the delegates from which were appointed by their respective governments. Its chief and most important distinction, however, was its restriction to the consideration of plans for securing international uniformity in strength of potent medicines only. As a result of this limitation of its scope, it is believed to have satisfactorily accomplished its task, and to have achieved a measure of success which was not possible with that wider range of discussion—involving such diverse topics as pharmaceutical education and titles, the regulation of the practice of pharmacy, and particularly the compilation of a complete international pharmacopœia—which had characterized and rendered ineffective all preceding pharmaceutical congresses.

The initiative for convening the recent Conference at Brussels proceeded from the Paris Congress in 1900, and was based upon a proposition offered by Professor Tschirch, of Berne, which, as finally adopted, was as follows:

"To have a comparative table prepared showing the differences in strength of medicaments bearing the same name in different pharmacopœias. To have this table distributed to the pharmacopœia commissions, to the academies of medicine and the pharmaceutical colleges and associations of the various countries, with the request to take this matter into due consideration at their next pharmacopœia revision, and to adopt, so far as possible, a uniform standard of strength, and where differences still remain, to call attention to such in foot-notes.

"To ask the Belgian Government to arrange with other governments a Conference in Brussels, and to ask all the delegates appointed to such a Conference to have their proposals ready to lay before the meeting whenever this may be called."

In accordance with this recommendation, and with a proposition emanating from the Royal Academy of Medicine of Belgium, the delegates appointed by the respective governments met in Brussels on September 15, 1902. The sessions were held in apartments

which were placed at the disposal of the Conference by the Belgian Government, and were in close proximity to the group of fine public buildings situated in the Rue de la Loi. The proceedings of the Conference were initiated by an address by Baron van der Bruggen, Minister of Agriculture and Hygiene, who, on behalf of the Belgian Government, extended a most cordial welcome to the delegates. This was responded to by Professor Gariel, of Paris, who, in the name of the delegates, nominated, as President of the Conference, Dr. A. Devaux, Inspector-General of the Belgian Department of Public Health and Hygiene. Mr. Van Hulst, of the Department of Public Health, was appointed Secretary, and Messrs. Heptia and Sterck served as Assistant Secretaries.

The various countries participating in the Conference were represented by the following delegates:

Austria-Hungary—Prof. August Vogl, Austria; Dr. Louis Toth, Hungary.

Belgium—Dr. A. Devaux, Prof. G. Bruylants, Prof. J. B. Depaire, Prof. A. Jorissen, Prof. J. F. Heymans, Prof. F. Ranwez, Mr. L. Van Hulst.

Bulgaria—Mr. Alexander Iv. Naidénovitch.

Denmark—Mr. H. J. Möller.

France—Prof. Gariel, Prof. Bourquelot, Mr. Yvon.

Germany—Prof. Binz, Prof. E. Schmidt, Dr. Rost.

Great Britain—Dr. Donald MacAlister.

Government of India—Lieut.-Col. J. Reid.

Italy—Senator Emmanuel Paterno di Sessa.

Luxemburg (Grand Duchy)—Dr. Fonck, Mr. Gusenburger.

The Netherlands—Prof. B. J. Stokvis, Dr. Van Itallie, Dr. Greshoff.

Norway—Prof. Poulsson.

Russia—Prof. W. A. Tikhomirow.

Sweden—Prof. S. Jolin.

Switzerland—Prof. Alex. Tschirch, Mr. C. Buhrer.

United States of America—Dr. H. C. Wood, Dr. F. B. Power.

The only absent delegates were: Prof. G. Pouchet, France; Prof. A. Damberghès, Greece; Dr. F. Schmid, Switzerland, and Count de Tovar, Portugal.

The proceedings of the first day consisted of a detailed explanation by the President of the objects of the Conference, which was followed by the submission of certain definite rules by which the

delegates were to be guided in their work; all of which were adopted.

The ensuing four days were occupied with a discussion of details relating to a list of potent medicaments which had been submitted to the delegates in the form of a preliminary draft, and for which it was proposed that a uniform standard of strength or precise definition of character should be decided upon. In the course of these proceedings some special propositions were presented for consideration by a few of the delegates. These were submitted in a previously elaborated and printed form by the delegations from the Netherlands, Switzerland and Greece, and comprised a considerable number of detailed suggestions. The delegate from Denmark, Mr. H. J. Möller, likewise submitted special propositions for the unification of the formulæ of tinctures and medicinal wines, and for the adoption of the normal drop counter of the French Codex of 1884.

It would naturally be impracticable in this place to attempt a detailed account of the various propositions submitted to the Conference, and the discussions thereon, which are contained in the official report of the proceedings. The latter, forming a volume of 156 quarto pages, in the French language, was published and distributed, with remarkable promptitude, about four weeks after the close of the Conference. With consideration, however, of the considerable number of those who may be interested in this subject, but to whom the official report may not be available, it would seem desirable to record the final recommendations of the Conference, as adopted at the closing session. These were as follows:

ARTICLE I.

It is proposed that the medicaments here enumerated should receive the following Latin designations, and that they should be prepared in accordance with the directions placed opposite their names.

Name of Medicament.	*Directions for preparation.*
Aconitum Napellus, *L.*	
Aconiti tuber seu Tuber Aconiti.	Only the tuber of the current year to be employed, in a dry state. In preparing the powder no residue should be left.
Aconiti tinctura seu Tinctura Aconiti.	To be prepared by percolation with alcohol of 70 per cent. by volume. This tincture to be standardized to 0·025 per cent. of total alkaloids by a method to be hereafter determined.

Name of Medicament.	*Directions for Preparation.*
Atropa Belladonna, *L.*	
Belladonnæ folium seu Folium Belladonnæ.	Only the dry leaf to be employed. In preparing the powder no residue should be left.
Belladonnæ tinctura seu Tinctura Belladonnæ.	To be prepared of 10 per cent. strength by percolation with 70 per cent. alcohol.
Belladonnæ extractum seu Extractum Belladonnæ.	A solid extract, containing about 10 per cent. of water, to be prepared by means of 70 per cent. alcohol. The alkaloidal strength will be subsequently defined.
Colchicum autumnale, *L.*	
Colchici semen seu Semen Colchici.	The seed only, not the corm, to be employed.
Colchici tinctura seu Tinctura Colchici.	To be made of 10 per cent. strength by percolation with 70 per cent. alcohol.
Digitalis purpurea, *L.*	
Digitalis folium seu Folium Digitalis.	The leaf of the second year to be employed. In preparing the powder no residue should be left.
Digitalis tinctura seu Tinctura Digitalis.	To be made of 10 per cent. strength by percolation with 70 per cent. alcohol.
Uragoga Ipecacuanha, *Baill.*	
Ipecacuanhæ radix seu Radix Ipecacuanhæ.	The powder to be prepared from the bark of the root, and the ligneous portion rejected. The powder should contain 2 per cent. of alkaloids.
Ipecacuanhæ tinctura seu Tinctura Ipecacuanhæ.	To be made of 10 per cent. strength by percolation with 70 per cent. alcohol.
Ipecacuanhæ sirupus seu Sirupus Ipecacuanhæ.	Prepare with 10 per cent. of the tincture.
Hyoscyamus niger, *L.*	
Hyoscyami folium seu Folium Hyoscyami.	The leaf only to be employed.
Hyoscyami tinctura seu Tinctura Hyoscyami.	To be made of 10 per cent. strength by percolation with 70 per cent. alcohol.
Hyoscyami extractum seu Extractum Hyoscyami.	A solid extract, containing about 10 per cent. of water, to be prepared by means of 70 per cent. alcohol.
Strychnos Nux vomica, *L.*	
Strychni semen seu Semen Strychni seu Nux vomica.	Should contain 2·5 per cent. of alkaloids.
Strychni tinctura seu Tinctura Strychni; Nucis vomicæ tinctura seu Tinctura Nucis vomicæ.	To be made of 10 per cent. strength by percolation with 70 per cent. alcohol. Alkaloidal strength 0·25 per cent.
Strychni extractum seu Extractum Strychni; Nucis vomicæ extractum seu Extractum Nucis vomicæ.	To be prepared by means of 70 per cent. alcohol Alkaloidal strength 16 per cent.

Name of Medicament.	*Directions for Preparation.*
Opii pulvis seu Pulvis Opii.	The powder to be dried at 60° C., and to contain 10 per cent. of morphine.
Opii extractum seu Extractum Opii.	Should contain 20 per cent. of morphine.
Opii tinctura seu Tinctura Opii.	To be made of 10 per cent. strength by percolation with 70 per cent. alcohol. Should contain 1 per cent. of morphine.
Opii tinctura crocata seu Tinctura Opii crocata seu Laudanum Sydenhami.	Should contain 1 per cent. of morphine.
Opii et Ipecacuanhæ pulvis compositus seu Pulvis Doveri.	Should contain 10 per cent. of Pulvis Opii.
Opii tinctura benzoica seu Tinctura Opii benzoica.	Strength in morphine 0·05 per cent.
Strophanthi tinctura seu Tinctura Strophanthi.	To be made of 10 per cent. strength by percolation with 70 per cent. alcohol; the seed not to be deprived of fat.
Sclerotium clavicepitis purpuræ *Tul.* seu Clavicepitis purpuræ *Tul.* sclerotium.	
Secale cornutum seu Ergotum secale.	Ergot not more than one-year old, and to be kept in its entire state.
Secalis cornuti extractum seu Extractum Secalis cornuti; Ergoti extractum seu Extractum Ergoti.	Prepare an aqueous extract, and take up the latter with 60 per cent. alcohol.
Secalis cornuti extractum fluidum seu Extractum fluidum Secalis cornuti; Ergoti extractum fluidum seu Extractum fluidum Ergoti.	Of 100 per cent. strength.
Acidum hydrocyanicum dilutum.	Of 2 per cent. strength.
Laurocerasi aqua seu Aqua Laurocerasi.	To contain 0·10 per cent. HCN.
Amygdalæ amaræ aqua seu Aqua Amygdalæ amaræ.	To contain 0·10 per cent. HCN.
Phenoli solutio seu Aqua phenolata.	Of 2 per cent. strength.
Arsenas sodii seu Sodii arsenas; Arsenicicum natrium seu Natrium arsenicicum.	The crystallized salt, containing 36·85 per cent. of arsenic acid.
Arsenicalis Liquor Fowleri seu Liquor arsenicalis Fowleri seu Kalii arsenicosi liquor.	To contain 1 per cent. of arsenious acid.
Ferri iodidi sirupus seu Sirupus iodeti ferrosi seu Sirupus ferri iodati.	To contain 5 per cent. of anhydrous ferrous iodide.

Name of Medicament.	*Directions for Preparation.*
Cantharidis tinctura seu Tinctura Cantharidis.	To be made of 10 per cent. strength by percolation with 70 per cent. alcohol.
Iodi tinctura seu Tinctura Iodi.	Of 10 per cent. strength, prepared with 95 per cent. alcohol.
Lobeliæ tinctura seu Tinctura Lobeliæ.	To be made of 10 per cent. strength by percolation with 70 per cent. alcohol.
Cocainum hydrochloricum.	The anhydrous salt.
Hydrargyri unguentum seu Unguentum Hydrargyri.	Of 30 per cent. strength.
Antimoniale vinum seu Vinum antimoniale; Stibiatum vinum seu Vinum stibiatum.	To contain 0·40 per cent. of tartar emetic.

ARTICLE II.

In future the following principles should be observed:

(*a*) A potent medicament should not be prepared in the form of a medicinal wine.

(*b*) Tinctures of potent drugs should be made of 10 per cent. strength, and by percolation.

(*c*) Fluid extracts of potent drugs should be of 100 per cent. strength.

ARTICLE III.

It would be expedient to adopt a normal drop counter, of which the external diameter of the dropping tube should be exactly 3 millimetres. In other words, at a temperature of 15° C., and with distilled water, 20 drops should be equivalent to 1 gramme.

It was decided that the proposals of the Conference, as above detailed, should be reported by the delegates as soon as possible to their several governmental authorities, with the recommendation that they be adopted at the next revision of their respective Pharmacopœias. The final protocol, having been unanimously approved, was signed on September 20, 1902, by all the delegates from the countries represented who were present at the closing session, with the exception of those from Germany. The delegates from the latter country had previously announced that, although their government was entirely in sympathy with the work of the Conference, their instructions did not authorize them to sign the protocol. The signatories were as follows:

Austria-Hungary:

Austria—Dr. Augusto Vogl.

Hungary—Dr. Louis de Toth.

Belgium—Alf. Devaux, J. B. Depaire, G. Bruylants, A. Jorissen, F. J. Heymans, Fernand Ranwez, L. Van Hulst.

Bulgaria—Al. I. Naidenovitch.

Denmark—H. J. Möller.

France—C. M. Gariel, Em. Bourquelot, P. Yvon.

Great Britain—Donald MacAlister.

British India—Jas. Reid.

Italy—Emmanuel Paterno di Sessa.

Luxemburg—Dr. Fonck, H. Gusenburger.

The Netherlands—B. J. Stokvis, L. van Itallie, M. Greshoff.

Norway—E. Poulsson.

Russia—W. A. Tikhomirow.

Sweden—Severin Jolin.

Switzerland—A. Tschirch, C. Buhrer.

United States of America—Frederick B. Power.[1]

It was somewhat to be regretted that the delegates representing the United States and Great Britain should have received from their respective governments the official intimation of their appointment but a few weeks before the opening of the Conference, as sufficient time was thus not available to enable them to formulate and present, in advance of the meeting, a more comprehensive expression of their views respecting the various subjects to be brought forward for discussion.

One of the subjects in this connection which had suggested itself to the writer as worthy of careful consideration was the desirability of adopting the well-defined active principles of certain drugs—alkaloids, glucosides, etc., in the place of their so-called galenical preparations. Such a proposal should naturally be consistent with existing knowledge respecting the physiological action of the drugs and that of the active principles that have thus far been isolated from them, and would thus have some well-recognized and positive limitations. The fact was therefore not overlooked that some valuable medicinal drugs are not represented, and cannot be replaced, by a single active constituent, even though the latter may be most useful in itself. This is notably the case with opium, which will

[1] Dr. H. C. Wood, who also represented the United States as a delegate, and took an active part in the deliberations of the Conference, was unable to be present at the closing session on account of arrangements for his homeward journey.

probably always have a place in the pharmacopœias, quite independently of the extended use of morphine. A similar condition exists with regard to rhubarb and a number of other drugs, which cannot as yet be replaced by any known constituent of them. There are, however, instances where such conditions do not exist, and where in the interests of medical science—to which pharmacy should always be contributory—pure and well-defined chemical substances may, with advantage, replace the crude drugs and the variable and sometimes worthless preparations, such as tinctures, extracts, etc., which are made therefrom.

The preliminary list of medicaments submitted to the Conference included, for example, *tincture of jaborandi*, but when the question of uniformity of strength was considered it was wisely decided to expunge it altogether. This step was taken in view of the fact that not only are the jaborandi leaves occurring in commerce extremely variable in alkaloidal content, but it is believed to be generally conceded that their therapeutic activity is fully represented by the alkaloid pilocarpine.

Cannabis Indica and its preparations were likewise unanimously excluded on account of their unstable and variable character and consequent uncertainty of action. It is unfortunate that this factor of instability should attend the originally active preparations of cannabis or its resin, such as cannabinol, and thus preclude the use of an otherwise valuable drug. The other drugs or preparations contained in the preliminary list, the recognition of which by the conference was not considered desirable, were the following: *Colocynth* (on account of not being sufficiently potent), *stramonium*, *squill*, *Pearson's solution*, *syrup of chloral*, *syrup of codeine*, *syrup of morphine*, *phosphorated oil*, *digitalin* and *aconitine*.

Gelsemium was proposed for adoption by the Dutch delegation, but was opposed by the majority of the continental delegates on the plea of not being sufficiently used. With consideration, however, of the potency of the drug, the fact that the tincture is recognized by both the United States and British Pharmacopœias, and that the preparations of these two widely used standards differ to the extent of 50 per cent. in strength, its exclusion would hardly seem justifiable.

Among other proposals of the Dutch delegation, the following principle was enunciated:

"With regard to active principles, alkaloids, glucosides, etc., the Dutch delegates propose to absolutely discountenance them for international usage so long as they cannot be obtained in a crystalline state and chemically pure."

Notwithstanding the proviso contained in this declaration, a strong protest was raised by the same delegation against the adoption of *aconitine*, which was based on the argument that the substances occurring under this name in commerce are variable in character, and that, being so extremely potent in a pure state, the use of the alkaloid was exceedingly dangerous and in some cases had been attended with fatal results. In the opinion of the writer the reasons advanced for the rejection of this substance are precisely those which, for the public safety, should have made its recognition by an international conference not only desirable, but even imperative. The British Pharmacopœia of 1898 has adopted a pure, crystalline aconitine, and the characters of this are believed to be so well defined that, if they were accepted as a standard, no difficulty whatever would be experienced either in the uniformity of its production or in its proper identification. It is, moreover, a question whether a permanent solution of such a pure, crystalline aconitine or one of its salts, of a strength corresponding approximately to a tincture of the drug and of international uniformity, would not only be safer but therapeutically more satisfactory than the galenical preparations of aconite at present in use. Inasmuch as the opinion was expressed by one of the delegates and supported by some others, that aconitine could not be properly defined, notwithstanding the precise melting point of the alkaloid and some of its salts as well as other characters, as stated in the British Pharmacopœia, it was decided by the votes of a majority of the delegates that the use of this substance should not be sanctioned by the Conference, and that the strength of pharmacopœial preparations of aconite should be based upon the determination of a fixed percentage of *total* alkaloid.[1]

It has been gratifying to the writer to know that his views on

[1] The committee appointed to decide upon the proportion of alkaloids that should be contained in aconite and belladonna and their preparations, consists of: Professors Schmidt, Tschirch, Bourquelot, Jorissen and Mr. Yvon. It is of interest to note in this connection that some of the large and progressive pharmaceutical manufacturers do not regard aconite as capable of accurate chemi-

the subjects above referred to, although considered more from a chemical standpoint, are quite in accordance with those recently expressed by two eminent medical men, one in England and the other in Germany.

Professor Cash, of Owen's College, Manchester, in an article entitled: "On the pharmacological action and therapeutical employment of pseudaconitine and japaconitine" (*British Medical Journal*, October, 1902, p. 1243), remarks as follows:

"Used inwardly, pseudaconitine and japaconitine, given in the proportions indicated, may be employed for moderating circulatory activity in some febrile states, for the relief of pain, and for other purposes which have been answered by the exhibition of aconitine. *It may be added that solutions of the alkaloids would be very preferable for employment to preparations of the plants which yield them, for in the latter the main alkaloids not only vary in proportion, but are often associated with other principles which have a somewhat neutralizing or qualifying effect.*"

Prof. Oscar Liebreich, of Berlin, in an article entitled: "On the therapeutic value of cantharidin" (*British Medical Journal*, October, 1902, p. 1231), says:

"Tincture of cantharides, even if prepared with the greatest care, cannot be regarded as anything but most uncertain in composition, and this is due to the fact that the active principle in cantharides varies between 0·3 and 0·6 per cent. *Moreover, I consider that, broadly speaking, a tincture is not a suitable form for administering exceedingly powerful drugs such as cantharides.* It was not until Robiquet succeeded in preparing the active principle of cantharides in a crystalline form that the therapeutic employment of this drug could be considered afresh."

It was not to be expected that at such a conference the decisions should be always in accordance with the views of individual delegates or in all respects unanimous, but, when the diversity of nations represented is considered, it must be said that the proceedings were characterized by a remarkable degree of harmony, and by a willingness on the part of every one to make such concessions as were possible in conforming with the wishes of the majority.

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cal standardization, and therefore depend entirely upon physiological tests. The determination of *total alkaloid*, as has been proposed, can certainly afford but a very imperfect indication of the value or therapeutic activity of aconite, in the form in which the drug is generally available.

In order to secure the permanency which is essential for the successful continuance and further development of the work of the Conference, the following resolution was unanimously adopted:

"The Conference expresses the desire that the Belgian Government should establish in Brussels a permanent bureau, and that the government of each country represented should designate a correspondent, preferably a member of its Pharmacopœia Committee, with whom the secretary might correspond directly for purposes of information and intercommunication, and thus contribute to the attainment of general pharmacopœial uniformity. This permanent institution might be styled the *Secrétariat international pour l'unification des pharmacopées.*"

In connection with this account of the more serious work of the Conference, it is deemed proper, as it is presumably not without interest, to refer to the extremely cordial reception extended by the members of the Belgian committee, to their generous hospitality, and to their thoughtfulness in every arrangement that could render the visit of the delegates a pleasant one. Excursions were made to Ghent and Louvain, where the universities and other places of interest were visited; to the Royal Chateau at Laeken, with which are connected large conservatories containing magnificent palms and other tropical plants; and to the Congo Museum in the pretty village of Tervueren. By no means least in interest was a visit to the Solvay Institute, which, in addition to the laboratories for biological and bacteriological work, contains a room designed as a memorial of the distinguished Belgian chemist, Stas. In it are contained his library, note-books, and the medals awarded him, together with many extremely valuable and interesting pieces of apparatus and specimens illustrative of his work, especially in connection with the determination of atomic weights. A banquet had been arranged for the closing day of the Conference, but was abandoned in consequence of the lamented death of the Queen of the Belgians on the preceding evening.

No better expression of the sentiments of the delegates could be given than is contained in the closing words of the address delivered on their behalf to the organizers and committee of the conference by Professor Binz, of Bonn:

"Et ainsi nous nous trouvons devant cette belle fin qui couronne les premières assises de notre conférence. Je résume les remer-

ciements que les délégués étrangers doivent aux collégues belges en leur disant; au revoir pour continuer l'œuvre utile que nous venons de commencer, au revoir sous la même présidence et le même secrétariat; au revoir dans la ville natale d'André Vésale, sous *l'augurium* de ses mânes augustes. *Quod felix faustumque summum numen esse iubeat.*"

The hope so felicitously expressed can, alas, not be fully realized, for but a week after the close of the Conference the sad news was chronicled of the death of one of the most active of the delegates—Professor Stokvis, of the University of Amsterdam. His genial temperament, nobility of character, and rare scholarly attainments inspired all who knew him with a feeling of sincere regard.

Notwithstanding the mutations that time must bring before another International Conference of this character may be convened, it is believed that the results thus far attained will afford such a measure of encouragement as to ensure a continuance of the work, and thus lead eventually to a more complete realization of its ideals.

LONDON, December, 1902.

INTERNATIONAL STANDARDS.

BY M. I. WILBERT,
Apothecary at the German Hospital, Philadelphia.

For more than thirty-five years a proposed International Pharmacopœia has attracted the attention of leading men in the medical and pharmaceutical professions of the civilized world.

The history of the various International Congresses and that of the accompanying attempts that were made to formulate an acceptable International Pharmacopœia has been ably recorded in several of the leading pharmaceutical journals. A very exhaustive and interesting account, by Frederick Hoffman, now of Berlin, Germany, will be found in the volume of the AMERICAN JOURNAL OF PHARMACY for 1901.

The reason why these earlier attempts at securing uniformity were failures is no doubt to be found in the fact that the leading spirits, in the International Congresses, essayed to do too much. The original idea, and the one that was clung to tenaciously for a number of years, was to formulate an authoritative work that would include

all classes of drugs and preparations and be capable of displacing the various national Pharmacopœias. It was expected to be in fact, as well as in theory, a Pharmacopœia for all nations.

Not until the meeting of the Seventh International Congress, held at Chicago, in 1893, was it proposed that the International Pharmacopœia be restricted to one including only the more potent remedies. This more practical idea, though heartily endorsed by the American Pharmaceutical Association, never materialized, and at the Ninth International Congress, Paris, 1900, the committee having this project in hand evidently made no report. There had, however, been considerable comment and discussion on the project, among others, at the meeting of the American Pharmaceutical Association, Baltimore, 1898.

At the International Medical Congress, Moscow, 1898, Professor Tschirch, of Berne, Switzerland, proposed that a conference of official delegates be convened, at the invitation of one of the European Governments, with a view of establishing some international standards that would be acceptable to all concerned. In the same year Professor Rommelaere communicated to the Royal Academy of Medicine of Belgium some views on the same subject. This communication, after considerable discussion, was referred to a committee to formulate some plan by which the desired result could be brought about. This committee in its report acknowledged the impracticability of substituting an international for the various national Pharmacopœias, but at the same time called attention to the possibilities of danger that are to be found in the wide variation in strength of the more potent remedies. This element of danger the committee proposed to obviate, by a mutual agreement, among the various authorities, to unite on uniform strengths and methods of preparing the more active preparations.

At the first meeting of the Ninth International Congress, Prof. A. Tschirch, of Berne, Switzerland, proposed that instead of an International Pharmacopœia, an international conference be convened to discuss and propose a system of international standards for adoption in the various national Pharmacopœias.

This proposition, after some debate, was referred to a special committee to report at a subsequent meeting. At the fourth session, this committee reported a plan for outlining the work of such an international conference, and to give it an authoritative or official

standing, it was proposed to ask the Belgian Government to invite other governments to send delegates to a proposed conference in Brussels, these delegates to discuss and, if possible, to agree on a system of uniform standards for the more potent remedies. The report was accepted, and the resolutions embodying the request forwarded to the proper authorities of the Belgian Government.

The Belgian Government, acting on the recommendation of this Ninth International Congress, sent invitations to the governments most interested, and in return received uniformly favorable replies, accepting the invitation to send official delegates to an international conference.

This conference assembled at Brussels, September 15, 1902, and was composed of official representatives of eighteen different countries. The proceedings have been referred to quite extensively in the various pharmaceutical journals, so that it will not be necessary to recapitulate them here.

The final agreement has been commented on quite favorably by the pharmaceutical journals of England, Germany, France, Austria, Switzerland and Belgium. As these are the countries where the most progressive work in the medical line is being done, it would appear as though this late conference were destined to leave some tangible results as a direct outcome of its deliberations.

That these recommendations are not above possible criticism must be admitted. That some of them will not meet with general approval is to be feared. How far and how they should be recognized in this country is the subject that should interest us greatly at the present time. With the eighth decennial revision of the United States Pharmacopœia probably in press, suggested changes at the eleventh hour must have more than the idle fancy or whim of an individual to give them weight or importance.

Let us inquire first as to the authority of the Pharmacopœial Revision Committee to recognize recommendations of this kind. The answer is definitely and positively stated in the list of instructions given the committee by the Pharmacopœial Revision Convention. Under the heading "Purity and Strength of Pharmacopœial Articles," we find the following: "Regarding the strength of diluted acids, tinctures and galenical preparations in general, it is recommended that the committee keep in view the desirability of at least a gradual approach, upon mutual concessions, towards uniformity

with similar preparations of other Pharmacopœias, particularly in the case of potent remedies which are in general use among civilized nations."

This would appear to answer the question without the peradventure of a doubt. It even makes it imperative on the committee to take cognizance of any definite offer for securing greater uniformity in the strength of galenical preparations, and particularly of such as are to be classed under potent remedies.

The next question that suggests itself is as to the advantages to be derived by a more general adoption of these proposed international standards. The need of greater uniformity will be recognized when we reflect on the rapidity with which medical literature is spread from one country to another. This will appeal to us more readily if we look through one of the more popular weekly medical journals and note the number of abstracts from all quarters of the globe. Medical journals in Europe, on the other hand, quote extensively from the medical literature of this country, and it is not at all uncommon to find that an abstract from an American journal reappears in another, actually credited to a foreign source. With this liberal interchange of views and experiences, particularly in view of the usual practice of confounding the source of origin, it would appear that similar standards would be imperatively necessary.

This, in our own case at least, is the more apparent when we reflect that the average physician in this country has little or no knowledge of the contents of our Pharmacopœia, or how its preparations differ in strength from those in use in other countries.

The wide variation in the strength of some of these preparations is illustrated in the accompanying table, giving the proposed international standard and the present strength in sixteen of the larger independent States. A few words in explanation of this accompanying table: The necessary data was taken from the latest (1902) edition of the "Universal Pharmacopöe," by Bruno Hirsch, and includes not only the most recent editions of the various national Pharmacopœias, but also the older supplement to the German and the supplement to the Dutch Pharmacopœia. This explains the reason why this table includes several preparations not found in the body of these respective national standards.

Let us consider the proposition of the International Conference more in detail. Of the general recommendations that will probably

not find favor in this country is the recommendation that both liquids, as well as solids, be weighed. The next is the recommendation that the potent tinctures be made with dilute alcohol, the strength of which is placed at 70 per cent. by volume. The objection to this recommendation will probably be the excessive high cost of alcohol, due to the high internal-revenue tax.

The actual strength, or rather the proportionate strength, of the different galenical preparations should meet with general favor. Let us review, for instance, the tinctures included in this list of potent remedies. The general proposition places the strength of the potent tinctures at uniformly 10 per cent. The advantage of this is that the resulting tincture can readily be made to represent the soluble extractive of the respective drug, while at the same time it bears a definite, uniform and easily remembered relation to the drug, so that a physician, knowing the dose of the drug, can readily calculate the corresponding dose of the tincture. The variability of our own U.S.P. tinctures is well illustrated by this table. A comparative study of these figures would appear to indicate that no concerted attempt had ever been made to arrange these preparations according to any fixed rule, either as to drug content or dose of finished product.

Tincture of opium is calculated on the permissible minimum content of morphine. This accounts for the abnormal figure given for the U.S.P. preparation (13 per cent.). Some of the other figures are of course only approximate—U.S.P. tincture of nux vomica and B.P. tincture of belladonna, for example, for which the respective Pharmacopœias give alkaloidal strengths.

The point we wish to call particular attention to is the wide variation in the strengths of these various tinctures. A very little thought on the possible results of a misunderstanding or a mistake will readily convince any one of the necessity of more general conformity to some one standard strength.

The wisdom of the selection made by the Brussels Conference must also be conceded, when we realize that more than 55 per cent. of the tinctures included in the above list conform to the standard of strength adopted by the International Conference.

As to the necessary changes in our own Pharmacopœia, there are but two preparations in which there could be any objection to the proposed change, on the plea that a change might prove dangerous.

These two exceptions are tincture of cantharides and tincture of strophanthus—two preparations but little known and certainly not very popular in this country at the present time.

The next item on the accompanying table, syrup of ipecac, is possibly open to the criticism of not coming within the strict definition of a potent remedy. There is, however, some force in the argument that at the present time there is decidedly too much variation in the strength of this particular syrup. This latter argument would certainly apply to the next item—syrup of iodide of iron. This varies all the way from the weak preparation of the Greek Pharmacopœia to the 10 per cent. strength of our own national standard. Some regulation as to the strength of this preparation would appear to be advantageous, in view of its widely extended use. In the case of the U.S.P. preparation it would necessitate the reduction of the strength one-half, thus doubling the dose. The preparation itself would probably be more acceptable — certainly more stable than the present U.S.P. syrup.

The proposed strength for diluted hydrocyanic acid will meet with general favor in this country, as it practically corresponds in strength with that official in the U.S.P. at the present time.

As to mercurial ointment, it may probably meet with the same objection as the syrup of ipecac. As a matter of fact, a 30 per cent. ointment would probably be more generally popular than is the 50 per cent. ointment official at the present time.

The remaining three items are practically identical in strength with those now official in the U.S.P. The possible exception is Dover's Powder. This would be from 20 to 35 per cent. weaker in morphine strength, using the proposed international strength of powdered opium as a basis of comparison.

Altogether, the proposed standards for galenical preparations are in line with the general trend for more uniform formulas, as is evidenced in the later editions of the various European Pharmacopœias.

The feeling of the leading men on the Continent of Europe was voiced by the veteran M. Binz, who, at the close of the sessions of the conference, in a speech thanking the Belgian Government, congratulated the Belgian delegation for so directing the proceedings, and presenting a program that was generally acceptable and will be immediately realizable.

TABLE SHOWING PROPOSED INTERNATIONAL STANDARDS COMPARED WITH PREPARATIONS NOW OFFICIAL IN VARIOUS NATIONAL PHARMACOPŒIAS.

	International.	U.S.P.	British.	German.	French.	Russian.	Austrian.	Italian.	Spanish.	Portuguese.	Belgian.	Dutch.	Danish.	Swedish.	Swiss.	Greek.
Tincture of aconite	10	35	5	10	20	10	10	10		20		10			10	
" " belladonna . . .	10	15	6		20	10	10		20	20	20	10			10	
" " cantharides . . .	10	5	1·25	10	10	10	10	10		10	20	10	10	10	10	16·5
" " colchicum seed .	10	15	20	10	20	10	10			20	20	10		10	10	16·5
" " digitalis	10	15	12·5	10	20	10	10	10	20	20	20	10	10	10	10	16·5
" " hyoscyamus . . .	10	15	10	10	20				20	20	20	10				6·5
" " iodine	10	7	2·5	10	7	10	6	8	6	10	8	8	5	5	8	5
" " ipecac	10			10	20	10	10		20	20	20	10		10	10	
" " lobelia	10	20	20	10	20	10	10	10		20	20	10	10	10	10	
" " nux vomica . .	10	16·5	10	10	20	10	10	10	20	20	20	10	10	10	10	
" " opium	10	13	7·5	10	15	10	10	10		5	8·4	10	10	10	0	16·5
" " " camphorated	0·5	0·52	0·46	0·5	0·45	0·5				0·5	0·5	0·5	0·5	0·5	0·5	0·5
" " strophanthus . .	10	5	2·5	10	20	10	10	5				5		10	10	
Syrup of ipecac	1	7		1	3	1	1	1	2	2		5			1	1·5
" " iron iodide	5	10	7·3	5	0·5	5	5·5	0.61	0·67	0·49	0·5	5	10	10	1	0·005
Hydrocyanic acid dilute . . .	2	2	2	2	1				10	10	2·5	2				2
Ointment of mercury	30	50	48·5	33	50	30	30	50	50	50	50	25	20	20	34	50
Solution of potassium arsenite	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Wine of antimony	0·4	0·4	0·4	0·4		0·4	0·4	0·4	0·46	0·5	0·5	0·4		0·4	0·4	0·48
Powder of ipecac and opium per cent. of opium	10	10	10	10	10	10	10	14·3	8·8	10	16	10	10	10	10	10

Among the views of the pharmaceutical press it may be permissible to quote an extract from the *Schweizerische Wochenschrift*, 1902, page 510, in which the editor says: "The twentieth of September, the day on which the agreement was signed, will be a memorable one in the annals of pharmacy—it marks the advent of a new era, the attainment of attempts covering nearly fifty years."

As stated above, the comments on the action of this International Conference have been uniformly favorable; in our own country, however, there appears to be a lack of appreciation for the importance of this particular move, and unless we are to be again accused of being backward and ultraconservative, it will be necessary for the American pharmacist to indicate in a decisive and positive way his appreciation of the necessity of adopting the recommendations of the Brussels Conference, in a general way, if not wholly and according to the exact letter of the agreement. Let the watchword be to "follow the spirit of the recommendations," even if it does not appear feasible to accept the exact wording of the protocol.

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THE PROPOSED INTERNATIONAL STANDARD TINCTURES OF POTENT REMEDIES.

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The menstruum that is to be used for making the proposed international standard tinctures is, in many cases, so different from that directed in the U.S.P. for similar preparations, that it was thought desirable to make a number of experiments to see what, if any, advantage might be derived from following implicitly the directions of the Brussels Conference.

It is well known that the tendency, in this country at least, has

always been to use as weak a menstruum as is possible to exhaust the drug, and still have an elegant and stable preparation.

The advantage that must be admitted in favor of the proposed international standard menstruum is, that it would be uniform in strength for all tinctures of active drugs that are made by percolation. In addition to this, the keeping qualities of the preparations themselves would be enhanced on account of the increase in alcohol content, and also because a menstruum of comparatively strong alcohol does not extract as much inert and useless material as one containing more water. In addition to this, the strength of these various preparations is of such a nature that it is comparatively easy to exhaust the different drugs by percolation with the directed menstruum.

Before reviewing the different preparations before us, it may be of interest to call attention to several general points that occurred to us while making the following samples. It is well known that air-dry drugs contain a variable amount of water, and that this can in turn be displaced by prolonged drying at a comparatively high temperature. To get at an approximate idea of the net loss of extractive, a sample of each drug was dried in a steam-box at a uniform temperature of 60° C., until, after two hours interval, there was no perceptible difference in weight. The same procedure was later adopted with the exhausted drug. The gross loss is, therefore, the difference in weight between the air-dry drug and the residue dried to constant weight, while the net loss is the estimated difference between the air-dry drug minus the per cent. loss on drying, and the residue dried to constant weight.

The difference in the amount of contained water is also of interest. Several experiments were made with each of the different drugs, and the averages only are given. In looking over the results given below it will be found that the highest loss was in the case of aconite root, while the lowest was in powdered opium. Several samples of powdered opium that were examined did not vary more than 1 per cent of their weight, even on exposure to the heat of the drying oven for considerable length of time. It will readily be seen, however, how important a factor this contained moisture might be. In subsequent discussions of the international commission this feature will, no doubt, be given proper attention and provisions made for eliminating possible sources of error.

One other feature that a review of the obtained results will reveal is that of estimating the drug content from the measure of the resulting preparation; these proposed international tinctures will average about 9 per cent. With the single exception of tincture of ipecac, the resulting preparations are elegant in appearance, quite permanent, and do not offer any particular difficulties in the methods of procedure.

With these preliminary explanatory remarks we may proceed to a more detailed examination of the various preparations before us.

Tincture of Aconite.—This preparation has been the source of considerable comment in various directions; nevertheless, it must be admitted to be the most desirable preparation of a particularly active and useful drug. As is well known, our own U.S.P. tincture of aconite is much more potent than any of the similar preparations official in other pharmacopœias. Ground or coarsely powdered aconite root lost, on drying, an average of 8 per cent of its weight; 100 grammes of the air-dry root lost, on percolation with the required 70 per cent. alcoholic menstruum, and subsequent drying in the manner described above, 40 grammes. Allowing 8 per cent. for the contained moisture, this would give us a net loss of 32 grammes of extractive to the menstruum. One thousand grammes of the tincture measured 1,104 c.c., while 1 litre of the same weighed 906 grammes, at 25° C. In this particular instance there is no difference in the composition of the menstruum, the present U.S.P. directing 70 per cent. of alcohol as a menstruum. There would, however, be a considerable difference in the average dose of the resulting preparations. The U.S.P. tincture of aconite is usually given in doses varying from 0·03 to 0·20 c.c., while the proposed international standard preparation could be given in doses of from 0·10 to 0·70 c.c., giving a much more tractable variation and quantities that will be more in harmony with the doses of other potent tinctures.

Tincture of Belladonna.—Belladonna leaves, coarsely powdered, lost on drying 4 per cent. of their weight; 100 grammes of the air-dry drug lost a total of 32·5 grammes to the menstruum of 70 per cent. alcohol, with subsequent drying, or a net loss of 28·5 grammes. One thousand grammes of the tincture measured 1,106 c.c., while 1 litre weighed 904 grammes, at 25° C. In appearance this proposed international tincture does not differ materially from

that now official in the U.S.P.; there is, however, a marked difference in the alcoholic strength of the prescribed menstruum, the present pharmacopœia directing U.S.P. dilute alcohol, while the international standard directs dilute alcohol containing 70 per cent. of alcohol. The dose would be about one-third more, or instead of being from 0·06 to 0·05, would be from 0·10 to 0·70, practically the same as that for international standard tincture of aconite. This correlation of doses is one of the strongest arguments in favor of adopting these proposed international standards, the relations existing between the drug and the resulting preparations being uniform and easily remembered.

Tincture of Cantharides.—This is one of the preparations to which objections might be raised, on the plea that the resulting tincture would be much stronger than that official in the U.S.P. In answer to this it might be said, however, that the preparation is but seldom used, not being very popular with the medical practitioners of this country. Ground cantharides lost 3 per cent. on drying, while the air-dried, powdered drug lost a total of 27·5 grammes to the prescribed menstruum, or a net loss of 24·5 grammes for each 100. One thousand grammes of the tincture measured 1,092 c.c., while 1 litre, at 25° C., weighed 900 grammes. The average dose of the U.S.P. preparation is from 0·20 to 1·00 c.c., while that of the international standard preparation would be from 0·10 to 0·50, or nearly the same as that of tincture of aconite or tincture of belladonna.

Tincture of Colchicum Seed.—Colchicum seed was accepted in preference to the root, on account of the greater content of the active alkaloid, and also because the seeds are more reliable and more uniformly active than the root. The ground seeds lost on drying 4 per cent. of their weight. The total loss of weight after percolating with the required menstruum was 24·3 grammes for 100 grammes, or a net loss of 20·3 grammes of extractive. The difference in the alcohol content of the menstruum is from 60 per cent. directed by the U.S.P., 1890, to 70 per cent. directed by the International Conference. One thousand grammes measured 1,104 c.c. and 1 litre weighed, at 25° C., 901 grammes. The dose of the international standard tincture would be about one-third greater, or about from 1·00 to 5·00 c.c. instead of from 0·60 to 4·00 as directed for the U.S.P. preparation.

Tincture of Digitalis.—There is nothing distinctive about this preparation with the possible exception of marked increase in the alcohol strength of the required menstruum, the U.S.P. directing a 50 per cent. dilute alcohol, while the international standard formula requires a 70 per cent. alcohol. Digitalis leaves lost on drying 5 per cent. of their total weight. The menstruum, followed by drying the residue, extracted a total of 44 grammes, or a net loss of extractive of 39 grammes to each 100 of the drug. One thousand grammes of the resulting tincture measured 1,107 c.c., while 1 litre weighed 905 grammes, at 25° C. The average dose of the international tincture would be from 0·30 to 2·00, instead of from 0·20 to 1·50 c.c., for the present U.S.P. preparation.

Tincture of Hyoscyamus.—This is another preparation that differs little in appearance from the present U.S.P. tincture, though about one-third weaker in drug content. The powdered leaves lost 6 per cent. on drying. The gross loss of extractive was 37·5 grammes, and the net loss 31·5 grammes for each 100 of air-dry drug. One thousand grammes of the tincture measured 1,102 c.c., while 1 litre, at 25° C., weighed 902 grammes. The average dose would be from 1·00 to 4·00 c.c. instead of from 0·60 to 3·00 as given for the present U.S.P. tincture.

Tincture of Iodine.—This is another preparation that would be slightly increased in strength. This increase would be of comparatively little importance, however, as the tincture is seldom given internally. It is well known that all tinctures of iodine change more or less rapidly, the rate of decomposition apparently depending on the temperature at which the preparation is kept rather than on the chemic effect of any actinic rays of light. This being acknowledged, this preparation should be directed to be prepared extemporaneously, or at least it should be made in small quantities. For this, a small circulatory apparatus of glass can be extemporized, by means of which the preparation can readily be made in from a half to one hour without shaking, or any further trouble than pouring the alcohol into a wide-mouthed bottle, and putting the iodine into a test tube perforated at the lower end, so as to allow free circulation of the solvent. By means of such a circulatory apparatus a 10 per cent. tincture is as readily made as one containing but 7 or even 5 parts in a 100. One thousand grammes of the international tincture of iodine measure 1,160 c.c., while 1 litre at 25° C., weighs

880 grammes, the solvent in this case being 95 per cent. alcohol, the same as that directed by the U.S.P.

Tincture of Ipecac.—This would be a new preparation to American physicians and one that would probably meet with considerable opposition. It was apparently introduced into the Proceedings of the International Conference with the object of having a preparation from which a uniform syrup of ipecac might be made. This latter, however, is so much weaker than our own syrup, that it is an open question whether or not it could possibly come under the appellation of a potent remedy. One other feature of this proposed tincture of ipecac is that it is to be made from the bark of the root of Rio ipecac, discarding the ligneous cord entirely. This latter direction, it will probably be found, will not be readily complied with, as there is considerable difficulty in separating the fragments of wood from the bark, even when the comminution is done in an iron mortar. To try this more fully, 120 grammes of ipecac root were comminuted in an iron mortar until 90 grammes of a moderately fine powder had been obtained. The residue, weighing nearly 30 grammes, still contained an appreciable quantity of the bark of the root, but the ligneous cord had been so broken that any further attempt at separating the bark would certainly have introduced a very considerable quantity of the woody fibre. It will readily be seen how extremely impracticable it would be to attempt to separate the bark from the wood in cases where the powdering is done by steam-driven machinery. In physical properties the resulting tincture did not differ materially from one made directly from powdered ipecac, as usually prepared for percolation. The powdered root lost 4 per cent. of its weight on drying, the total loss of 100 grammes was 28 grammes or a net loss, allowing for the contained water, of 24 grammes. One thousand grammes of the resulting tincture measured 1,108 c.c., while 1 litre, at 25° C., weighed 900 grammes.

Tincture of Lobelia.—This is another preparation that differs little in general properties from the official U.S.P. preparation. There is of course a reduction of 50 per cent. in the drug content, and an increase in the strength of the menstruum, the present U.S.P. directing a 50 per cent. alcohol to exhaust the drug, while the international standard would require a 70 per cent. alcohol. Lobelia lost 4 per cent. of its weight on drying, while 100 grammes of the air-dry drug gave a gross loss of 28·6 or a net loss of 24·6 grammes

of extractive. One thousand grammes measured 1,106 c.c. and 1 litre, at 25° C., weighed 903 grammes. The average dose would be about double that of the present tincture, so that instead of giving from 0·30 to 1·00 c.c. we could give from 0·50 to 2·00 c.c.

Tincture of Nux Vomica.—It is well known that the present U.S.P. directs that this tincture be made from a solid extract, and has standardized the same to correspond to about 0·30 per cent. of total alkaloids. This is admittedly a rather roundabout way of accomplishing a simple feat, and has resulted in the rather peculiar complication that this preparation differs probably more than any other one in appearance and other physical properties.

The international standard tincture of nux vomica is to be made from a drug containing 2·5 per cent. of total alkaloids. This quality of nux vomica is readily obtained and a very acceptable preparation, completely representing the active qualities of the drug, is easily made by following the directions and using the menstruum indicated for the international standard preparation. Nux vomica lost 7 per cent. on drying to constant weight, while after exhausting with 70 per cent. alcohol and drying, it was found to have lost 23·5 per cent. or a net loss of 16 5 grammes for each 100 of the drug employed. One thousand grammes of the tincture measured 1,108·5 c.c., and 1 litre weighed 896 grammes at 25° C. The average dose of the international standard preparation would be from 0·50 to 2·00 c.c. instead of 0·40 to 1·50 c.c., as at present.

Tincture of Opium.—The International Conference adopted a powdered opium with a morphine content of 10 per cent. This would make an average difference of about one-third in the U.S.P. preparations of opium. The proposed tincture of opium is standardized to contain 1 per cent. of morphine. This change would increase the average dose of this tincture to from 0·50 to 2·00 c.c. for the international tincture, instead of from 0·40 to 1·50 for the present U.S.P. preparation. Powdered opium appears to contain but little extraneous moisture, the average, even on long-continued heating, being but 2 per cent., the drug losing a total of 68 per cent. to the prescribed menstruum of 70 per cent. alcohol, or a net extractive of 66 per cent.; 1,000 grammes of the international standard, standardized tincture measured 1,108 c.c., while 1 litre of the same at 25° C. weighed 908 grammes.

Tincture of Strophanthus.—This preparation, like that of canthar-

ides, would be practically doubled in strength. This is, however, also like that of cantharides, not of serious moment, as it is not very popular, and not extensively used, probably due largely to the fact that little really first class seed finds its way to this market. In the matter of dosage, the increase in the drug-strength would bring this preparation in the class with aconite, belladonna and cantharides. The average dose would be from 0·10 to 0·50 instead of from 0·20 to 0·80 c.c. as given for the present U.S.P. tincture. A good quality of the ground drug lost 4 per cent. on drying, while after exhaustion with 70 per cent. alcohol and subsequent drying it was found that 100 grammes had lost a total of 32 grammes, or a net loss of 28 grammes of extractive; 1,000 grammes of the tincture measured 1,108 c c., while 1 litre, at 25° C., weighed 896 grammes. The resulting tincture, without any previous preparation of the seed, is of a golden yellow color and appears to be quite stable, remaining clear and transparent.

Altogether it may be said that the proposed international standard preparations are readily made, and give uniformly satisfactory preparations. With the possible exception of the tincture of ipecac, they should receive the consideration and recommendation of members of the medical as well as pharmaceutical profession, so as to have them properly presented before the members of the United States Pharmacopœial Revision Committee for their consideration and adoption.

THEOCIN, THE FIRST VEGETABLE ALKALOID MANUFACTURED ON A LARGE SCALE BY SIMPLE SYNTHESIS.[1]

By Dr. Hugo Schweitzer, New York City.

In 1888 Kossel found in the extract of tea-leaves a new alkaloid isomeric with theobromine, to which he gave the name of theophylline. It was present in such exceedingly small quantities, however, that it could not be tested even for its pharmacological properties. But when E. Fischer succeeded in synthesizing the bodies belonging to the purin class, it became possible to study theophylline from a therapeutic standpoint. It was found that it was the most power-

[1] Read before the New York Section of the American Chemical Society, December 5, 1902.

ful diuretic of this class of vegetable alkaloids. By the synthesis of Fischer somewhat larger quantities could be prepared, but at a tremendous expense. It was the endeavor of chemists interested in this branch of chemistry to find a way of preparing this valuable remedy so that it could be used commercially.

I am exceedingly pleased to state that such a synthesis was at last discovered in the laboratories of the Farbenfabriken of Elberfeld. The new synthesis is based upon Wilhelm Traube's research, published in the *Berichte der Chemisch. Gesellsch.*, Vol. 33, p. 3053, 1900. The modifications of this process enable the Farbenfabriken to produce in about twelve reactions the alkaloid, which is named by them theocin, on a larger scale, and at a price which makes its introduction into medicine feasible.

Although some vegetable bases and alkaloids had been previously produced—thus Ladenburg prepared coniin, Hantzsch trigonelline and Willstaetter cocain—yet a complete synthesis like that of theocin has not hitherto been accomplished on a commercial scale.

This synthesis must, therefore, be considered as one of the most remarkable achievements of organic chemistry, both from the technical and scientific point of view, and can justly be compared with the synthesis of indigo.

There were several reactions known which led to the formation of indigo, but none was economical; it was the Badische Anilin and Soda Fabrik which first discovered a process for the manufacture of this vegetable product by synthesis. The same is true of theocin: there was the "Fischer," the "Traube" reaction; there was the "Fischer and Ach" modification of the "Fischer" synthesis, yet none of these reactions could be carried out on a commercial basis. The Farbenfabriken process is the first one by which this vegetable alkaloid can be manufactured on a large scale.

The value of the synthesis of theocin will be seen from the fact that while the natural product cost $93 an ounce, the price of the synthetic preparation is $2.30.

In regard to its physical and chemical characters the following may be said: Theocin appears in the form of beautiful colorless needles, having a melting point of 268° C. It is difficultly soluble in cold water and alcohol, but more readily in warm water; insoluble in ether. It is, however, much more soluble in cold water than

theobromine, dissolving in the proportion of 1 to 179 parts as compared with 1 to 1,600. Theocin forms salts, of which the ammonium and potassium salts dissolve readily, while the sodium salt is only slightly soluble.

You may ask why theophylline was rechristened "theocin." The product is intended to be used in medicine, and for this reason it was given the new name to distinguish it from the natural product. There are to-day any number of physicians who still think that synthetic products do not possess the same medicinal properties as the natural bodies; for example, even the purest synthetic salicylic acid is by many considered inferior to salicylic acid made from oil of wintergreen, which latter also commands a vastly higher price. You know that hosts of people think that beet sugar is not as sweet as cane sugar. To avoid misunderstandings, therefore, synthetic theophylline has been named "theocine."

As you are aware, the only members of the purin group that have been employed in medicine are caffeine and theobromine. Caffeine is used as a heart stimulant and diuretic, and as a remedy for headaches; theobromine chiefly as a diuretic. Both of them act directly upon the kidney, but theobromine is more powerful in its action, and is devoid of the exciting effect of caffeine upon the nervous system and its stimulating influence upon the heart. Owing to the fact, however, that it frequently causes stomach disturbances it is chiefly prescribed in the form of its double salts—diuretin and agurin.

According to the clinical experiments of Prof. O. Minkowski, of Cologne (Therapie der Gegenwart), theocin approximates more closely in its action to theobromine than to caffeine. It is practically devoid of any effect upon the heart or circulation, and exerts a much more decided diuretic action than theobromine. Under its administration the pulse and blood pressure were not affected, and no irritation of the kidneys was noted, which is, of course, a very important point in the class of cases in which it is indicated. Professor Minkowski tested theocin in various conditions of dropsy due to affections of the heart, liver and kidneys, and found that in most instances the daily quantity of urine under its use ranged from 3,000 to 5,000 c.c. In one instance the increase was remarkable—from 1,300 c.c. to 7,600 c.c. in the twenty-four hours; and in connection with this there was a complete disappearance of the dropsy during

that period, although previously it had not yielded to other remedies. In fact, his experience showed that theocin was of particular value in cases in which there were extensive dropsical effusions. Examinations of the urine by Professor Dreser showed that not only the quantity of the fluid but also of the solid constituents was augmented.

From a medical point of view, therefore, the discovery of a cheap means of preparing theophylline is of great interest, since it places at the disposal of the medical profession a new diuretic of greater efficiency than those in previous use, and thus contributes to a more successful treatment of various conditions in which dropsy is a prominent symptom.

It may also interest you to know that synthetic theobromine will shortly be introduced into medicine.

THE PRESENCE OF ARSENIC IN CHEMICALS.

By Lyman F. Kebler.

The immediate reason for this investigation was the unfortunate wholesale poisoning in Manchester, England, about two years ago. At first it was thought this poisoning was due to the alcohol imbibed by the excessive drinking of beer; but investigation showed that the poisoning was probably not due to the alcohol, but rather to the arsenic contained in the beer. That is, the poisoning, instead of being alcoholic neuritis, was arsenical neuritis, or perhaps a mixture of both; the source of the arsenic being arsenical glucose, which was used in the manufacture of the beer; the glucose in turn being prepared by the intervention of arsenical sulphuric acid.

When this fact became known, nothing was more natural than that other products, in the preparation of which sulphuric acid is employed, should be investigated. The chemical and medicinal remedy, which is used in such large quantities by the laity, is sodium phosphate. This product was carefully examined, both abroad[1] and in this country,[2] and found to contain more or less arsenic. One sample of the imported material was found by the author to contain 1 milligramme of arsenous oxide in 5 grammes of

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[1] 1900, *Chemist and Druggist*, 58, 1034.
[2] 1900, *American Druggist*, 37, 103.

the chemical—an amount which certainly might cause alarming symptoms when taken *ad libitum*.

In 1775 Scheele[1] made the important discovery that arsenic united with hydrogen to form a fœtid gas was decomposed by heat. Proust[2] observed that this same gas was disengaged when arsenical tin was dissolved in hydrochloric acid, and arsenic was deposited when the inflamed gas was brought against a cold surface. Trommsdorf[3] next announced that arsenical hydrogen was evolved when arsenical tin was treated with dilute sulphuric acid, and if this gas was passed through a sufficiently long tube, arsenic was deposited on its walls. Arsenical hydrogen was further studied by Davy, Gay-Lussac, Gehlen, Stromeyer, Thenard; and Serrullas in 1821 proposed to utilize the above reaction for a toxicological test.

In 1836 Marsh[4] published his celebrated memoir, entitled "Account of a Method of Separating Small Quantities of Arsenic from Substances with which it may be Mixed." He elaborated and simplified the apparatus, generated hydrogen by means of dilute sulphuric acid and zinc, inflamed the escaping gas, and deposited the arsenic in the form of metal, which afterward could be converted into arsenous oxide. This brief review amply shows that Marsh was not the discoverer of the arsenic test, which is usually called by his name, but like many other useful processes and inventions, it seems to have been gradually evolved by the combined efforts of many minds. This, however, must be said: Marsh was the first to simplify and prominently bring forward the test very much improved, if not perfected.

Little, probably, did these early investigators think that this method would be more thoroughly investigated than any other process in the realms of chemistry.

Many other methods have been suggested from time to time, but not one of them as yet has been proved the superior or even the equal of Marsh's test modified in one form or another.

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[1] 1775, Memoires de Scheele, t. I, 170: Om Arsenick och dess Syra; Kongl. Svenik. Vatenikops Academiens Handlingar: Ar. 1775, V. 36, 265.

[2] 1798, *Ann. de Chem.*, 28, 213; 1800, *Jour. de Phys. et Chem.*, 51, 173.

[3] 1803, *Nicholson's Journal*, 6, 200; from Royal Academy of Sciences, Berlin, p. 370.

[4] 1836, *The Edinburgh New Philo. Journal*, 21, 229; 1837, *Jour. de Pharm.*, 23, 553; *Ann.* (Liebig), 23, p. 207.

The method next important to Marsh's is undoubtedly Reinsch's,[1] in which metallic copper is employed to deposit the arsenic, which it is claimed forms a definite chemical compound with the copper $Cu_6 As_2$. Fleitman's[2] method is practically a modification of Marsh's test, in which the hydrogen is generated by means of an alkaline solution, acting on metallic aluminum or zinc. By Bettendorff's[3] method, the arsenic is deposited as a metal, in a stannous chloride solution, upon metallic tin. Gutzeit[4] utilized the well-known reactions of arsine on paper moistened with a solution of mercuric chloride, or acidulated silver nitrate.

The last three methods are the ones employed by the U.S.P. to detect arsenic in the compounds recognized by it. The object in employing these methods was primarily because they were comparatively simple and at the same time gave fairly accurate results. When it is a question of testing for the presence of arsenic in any compound, nothing short of the very best available method should be applied; inasmuch as it so frequently happens with rapid methods, they give inaccurate reactions and leave the worker in doubt. For example: Gutzeit's test is evidently superior in point of delicacy to even Marsh's or Reinsch's, but depending on the formation of a yellow compound, by the action of arsine on mercuric chloride or acidulated silver-nitrate solution the results are ambiguous, because of the fact that very minute traces of hydrogen sulphide or phosphine produce a stain similar to the one produced by arsenuretted hydrogen, and there is no means of distinguishing between them.

It is the experience of chemists in general that the Marsh test modified by Berzelius, and the Reinsch method are the most reliable, some being in favor of one method and others in favor of the other. After considering the various methods in detail and making some experiments with the same, it was decided to compare Bettendorff's methods with the two above.

Before attempting to apply the tests, it is important to ascertain whether the chemicals and every part of the apparatus to be employed are relatively free from arsenic or other interfering agents. The word "relatively" is used because chemists realize that it is

[1] 1842, *Jour. de Pharm.*, 2, 361.
[2] 1851, *Ann.* (*Liebig*), 72, 126.
[3] 1869, *Ztsch. für Chemie*, 12, 492; *Wittstein's Vierteljahrschr.*, 1870, 430.
[4] 1879, *Pharm. Ztg.*, p. 263.

practically impossible to obtain many articles at present absolutely free from arsenic.

There is always more or less trouble with the metallic zinc to be employed in the Marsh-Berzelius method. The Joint Arsenic Committee of the Societies of Chemical Industry and Public Analysts[1] in connection with the preparation of standard mirrors, states: "It is important to note that some 'pure' zinc is, from a cause at present unknown, not sufficiently sensitive; that is to say, the addition of minute quantities of arsenic produces no mirror." Various methods have been suggested for overcoming this difficulty; for example, platinum chloride is added; A. H. Allen[2] recommends that a trace of iron be always present; W. Thompson[3] uses copper sulphate and says that nickel is better.

O. Hehner[4] claims that platinum chloride makes the reaction less delicate. Headden and Sadler[5] get much lower results on the addition of copper sulphate or platinum chloride. Investigations are needed along this line.

The zinc employed in this work was prepared electrolytically, and a careful test of the same showed that it was free from arsenic, but contained a minute trace of iron, the latter probably coming from the vessels in which the zinc was molten for granulation. The influence of iron on arsenic will be discussed under the iron compounds.

O. Hehner[6] prepares arsenic-free zinc as follows: melt ordinary block zinc in a clay crucible, when quite fluid, add, for each pound of zinc, about 1 gramme of metallic sodium, and stir well with a glass rod. A black scum forms immediately. Remove scum from time to time as formed by means of a china spoon or crucible cover held in tongs. When the metallic sodium appears to be oxidized, add more sodium, again stir vigorously and remove scum formed. The above operation takes about ten minutes. Now pour the molten zinc into a second clean clay crucible and treat with metallic sodium as above; finally allow the molten metal to cool considerably, then granulate in the usual way.

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[1] 1902, *Jour. Soc. Chem. Ind.*, 21, 95.
[2] 1902, *Jour. Soc. Chem. Ind.*, 21, 94.
[3] 1902, *British Food Jour.*, 4, 193; *Chem. News*, 86, 179.
[4] 1901, *Jour. Soc. Chem. Ind.*, 20, 194.
[5] 1885, *Am. Chem. Jour.*, 7, 338.
[6] 1902, *Jour. Soc. Chem. Ind.*, 21, 675.

It is not so very difficult to obtain sulphuric acid comparatively free from arsenic; but the first sample secured contained quite an appreciable quantity of the arsenic; a second sample proved to be very good. For testing the acid, 30 c.c. were diluted to 150 c.c. and poured through the separatory funnel, a little at a time, so that the evolution of gas could be regulated.

There appeared within fifteen minutes after the hydrogen current became uniform a very faint yellowish-brown spot in the constriction of the tube. This did not increase even after one hour of continuous evolution of the gas. The spot was probably due to a mixture of sulphur and arsenic. Inasmuch as only 12 c.c. of the sulphuric acid were employed for each subsequent operation, and the apparatus was tested in each case for thirty minutes before introducing the material to be tested, this small coloration could be entirely neglected. As a matter of fact, 12 c.c. of the concentrated sulphuric acid, diluted, did not produce a coloration sufficient to be seen with the naked eye.

No hydrochloric acid could be obtained that was free from arsenic. It was, however, prepared by distilling the purest obtainable article with ferrous chloride, rejecting the first tenth that came over. This procedure gave an acid which was free from arsenic when tested thoroughly with the three methods used.

The tin and copper foils, as well as the calcium chloride, were examined and found to be free from arsenic.

The Marsh-Berzelius apparatus consisted of a 200 c.c. Erlenmeyer flask, provided with a double perforated rubber stopple, carrying a 50 c.c. separatory funnel and exit tube, which was connected with a straight, bulbed, calcium-chloride tube, the latter being nearly filled with pure anhydrous calcium chloride. At the end of the calcium-chloride tube, toward the Marsh tube, there was placed a wad of cotton so as to prevent a flashing back of the flame into the apparatus, and thus avoid explosions. The separatory funnel was employed because the amounts to be used could be carefully regulated and the danger of introducing air was eliminated.

The hard glass Marsh tubes (free from arsenic, lead and antimony) were drawn out with two constrictions of the conventional diameter, and the far end was also drawn out fine and fused so as to leave only a small orifice. This precaution prevented any further fusion of the glass by the burning hydrogen.

About 25 grammes of zinc and 60 c.c. (1 to 5) of sulphuric acid were used for each operation. That is, the apparatus was thoroughly cleaned each time a new test was made.

Bettendorff's reagent was made by dissolving pure tin foil in concentrated hydrochloric acid; the tin was added until the solution was thoroughly saturated. In applying this reagent, all solutions were highly acidulated with hydrochloric acid.

Reinsch's method was applied in the usual way, no special precautions being necessary, except when organic matter was present or other interfering agents were indicated.

A careful comparison of these methods with known material gave the following results:

Mg of As_4O_6.	Grains of As_4O_6.		Marsh-Berzelius.	Reinsch's.	Bettendorff's.
1.—1.	1/65	=0.0154	Color black immediately.	Foil black almost instantly. Crystals many and large.	Considerably less gave a decided reaction.
2.—0.5	1/129	=0.0077	Color black immediately.	Foil black almost instantly. Crystals many and large.	Considerably less gave a decided reaction.
3.—0.25	1/260	=0.00385	Color black immediately.	Foil dark gray. Crystals large and many.	Tin-foil and solution colored within two minutes. Bad in fifteen minutes.
4.—0.125	1/520	=0.00192	Color lighter black in two minutes than No. 3.	Foil dark gray. Crystals large and many.	Not so intense a coloration as No. 3.
5.—0.0625	1/1037	=0.00096	Color lighter black in five minutes than No. 3.	Foil much colored, crystals plain.	Solution and tin show coloration within fifteen minutes.
6.—0.03125	1/2074	=0.00048	Color lighter than No. 5; time, seven minutes.	Foil assumes dark purple color. Crystals plain.	Color did not show up within fifteen minutes. After twenty-five minutes, slight coloration of tin-foil.
7.—0.01562	1/4149	=0.00024	Color lighter than No. 6; time ten minutes.	Foil slightly colored purple. Crystals plain.	After an hour there seemed to be a slight coloration.

8.—0.00781	1/8298 =0.00012	Stain quite marked in one-half hour.	Foil but little colored. Crystals plain.	Results negative.
9.—0.00390	1/16596=0.00006	Stain less marked than No. 8.	Foil very slightly colored. Very few crystals.	Results negative.
10.—0.00195	1/33333=0.00003	Stain faint in one-half hour.	Slight stain. No crystals.	Results negative.
11.—0.00129	1/50000=0.00002	Stain very faint in one hour.	Slight stain.	Results negative.

These figures are only approximately equivalent.

According to the above results the limit of the Bettendorff test is about 1-30 milligramme or 1-2000 of a grain of arsenous oxide per cubic centimetre of solution or gramme of material. The limit of the Reinsch's method is reached at about 1-260 of a milligramme or 1-17000 of a grain of arsenous oxide in 1 c.c. of solution or 1 gramme of material. The limit of the Marsh-Berzelius test is reached at about 1-512 of a milligramme or 1-33333 of a grain of arsenous acid per cubic centimeter of solution or gramme of material.

It is claimed by some observers that the 1-1000 of a milligramme per cubic centimetre of liquid gives positive indications, but some of the more conservative are of the opinion that 1-10 of a milligramme per cubic centimetre of fluid is about the limit. The evidence of the presence of 1-512 of a milligramme of arsenous oxide per gramme of material obtained by the writer is not at all positive, and he is of the opinion that considerably more must be present before the chemist can make a positive statement; 1-10 of a milligramme is, however, a little too conservative, because with this amount the tube becomes almost black throughout the constriction.

It was decided to make standard tubes or mirrors for the Marsh-Berzelius test by depositing the metallic arsenic in the tubes and using them for comparison in deciding as to how much arsenic a given substance contained. This was decided on, because it was soon found, after a little work was done, that it was practically impossible to weigh the small quantities of arsenic generally obtained. The figures given above represent the amount of arsenous oxide contained in one or more cubic centimetres of solution of known

strength. The solutions were consecutively so diluted that the writer was in a position to know just how much arsenic was added in each operation, and carried to such an attenuation that only the minutest coloration was developed in the reactions.

On comparing the above results with those obtained by other observers, it can be readily seen that the Marsh-Berzelius test did not appear to be as delicate as frequently represented. The writer thinks, however, that this is chiefly due to the fact that, with few exceptions, experimenters have given the degree of dilution of the solution without mentioning the quantity employed. The point made by the late Dr. Wormley[1] in this connection is well worth repeating. He says: "Thus, it has been stated that the method (Marsh) will yield satisfactory deposits when the solution contains only 1-2,000,000th of its weight of arsenic. This is true, but it requires about 1,000 grains of such a solution to furnish these results; the absolute quantity of oxide present would, therefore, be about 1-2000th of a grain."

In preparing the standard tubes, it is desirable to make two or more so as to be certain that the tubes are alike and uniformity exists in the operation. It is possible that the standard tubes of one worker will vary slightly from those of another, but this will not materially affect results if details are observed. The tubes must be prepared from the same zinc and reagents subsequently to be employed for the work.

How long the tubes will be reliable, time only can tell. Those in the writer's possession, made over a year ago and carefully sealed, show by comparison with new tubes not to have changed in the least.

After making a careful study of the above three methods, both as to reliability and ease of execution, it was decided to employ the Marsh-Berzelius method throughout. This process is frequently decided against as being too difficult of operation. Such an objection is probably justified, but it is the writer's experience that when pure reagents are at hand, and the apparatus is once set up, the results are obtained with less attention and trouble than by any other method.

It is always wise to make two mirrors—one for comparison with

[1] 1885, "Microchemistry of Poisons," 2d Ed., p. 285.

the standard and the other for the production of octahedral crystals of arsenous oxide. This precaution is essential to eliminate the possible presence of such disturbing impurities as antimony, mercury and selenium.

When comparatively large deposits of antimony are heated, the resulting sublimate may contain octahedral crystals.[1]

Selenium and tellurium have been discussed by A. E. Berry[2] and O. Rosenheim.[3] Tellurium probably has no influence on the Marsh-Berzelius test, but there seems to be much uncertainty at present about the influence exerted by the selenium. The disturbing influence of this element can be eliminated, like the sulphur compounds, by placing a wad of cotton, moistened with lead acetate, in the forepart of the calcium-chloride tube.

The arsenical deposit occurs from 1 to 2 centimetres back of the flame, which is so placed that the greater portion of the mirror is in the constriction of the tube. When the deposit is small, a fine brownish mirror results, but large deposits are arranged in three rings. The ring toward the flame is brown and semi-transparent. The middle portion is dense and almost black, while the outer portion is grayish and diffusing.

The character and formation of the mirrors are influenced by certain elements like antimony, mercury and selenium.

As above stated, the hydrogen was allowed to evolve slowly and pass through the apparatus for thirty minutes before the substance to be tested was introduced. The flame during this time was placed just before the outer constriction; and if any arsenic could possibly have been present in any portion of the zinc, sulphuric acid, etc., it would have been revealed by this precaution. The test, however, was invariably negative. The flame was then placed just before the inner constriction and the substance, or solution of the substance to be tested, introduced into the flask, little by little, through the separatory funnel. It is generally necessary to add the substance to be tested slowly, because the presence of arsenic seems to augment the reaction very materially. In most cases where arsenic was present, it was revealed in from five to eight minutes, and all seemed to have been evolved in from fifteen to twenty minutes. The test, however,

[1] Wormley, 1877, *Am. Jour. Med. Science*, 74, 399.
[2] 1901, *Jour. Soc. Chem. Ind.*, 20, 322.
[3] 1901, *Chem. News*, 83, 280.

was uniformly continued for thirty minutes. In a few doubtful cases the hydrogen was permitted to be generated for one hour. It was considered that a longer time than this was absolutely unnecessary, inasmuch as chemists realize that if large enough quantities are taken, and the reaction allowed to continue sufficiently long, a trace of arsenic can be obtained from almost all substances.—*Read at the A.Ph.A. meeting, September, 1902.*

PHARMACEUTICAL AND CHEMICAL NOTES.

By Clement B. Lowe.

I have some matters of interest to bring before this meeting this afternoon which I hope will be of some practical value.

The first is a blank form which I have had printed for keeping a record of prescription renewals. It largely explains itself. At the close of the day's business the column entitled, "Renewal No.," which has been left blank, is filled in by the numbering machine. At the end of the year the prescription number represents the exact number of prescriptions compounded during the year. This plan of keeping account of renewals helps us greatly in keeping our numerous charge accounts straight, and also in renewing prescriptions.

PELHAM PHARMACY.

Prescription Renewals . . . . . mo. . . . . day, 190 . .

No.	Renewal No.	Number.	Date.	Doctor.	Price.
1.					
2.					

Whenever I attend a pharmaceutical meeting I try to bring away from it something of value, be it small or great. Acting upon the suggestion of Mr. Ruhl, of Manheim, as presented at the Pennsylvania Pharmaceutical Meeting, I show you a three-cornered file, and the deft manner in which, by means of it, a cork can be extracted from a bottle. Owing to its shape, it has the disadvantage of being hard to pick up. Another suggestion which I show you is the cap of a castor-oil can, which has had a round hole cut in it and a tin tube soldered to it, so that the oil can be poured out without spilling a drop. This cap will fit all cans of the same make.

I also exhibit a wine of coca leaf (30 grains to the fluid ounce) in which the menstruum is muscatelle wine, this making a more agreeable preparation than claret wine.

A neat and quick way (first suggested by Professor White) for determining whether a change has taken place in bichloride of mercury gauze, by which it may have been partly changed into the mild chloride (calomel), is to pour limewater upon a small piece. If a black color is produced, the change has taken place.

In our investigations we sometimes jump at conclusions. Last winter, whenever I used a certain mortar and pestle (the latter of which had a hard rubber handle) for triturating, especially calomel and sugar, a peculiar crackling sound seemed to be produced, like that of the "electricity of friction" made by drawing a hard rubber comb through the hair, etc. I repeated the experiment a number of times; each time the sound was produced, the rubber handle apparently acting as a non-conductor. Just about the time that I thought I had made a discovery, I found that the pestle was hollow, and the peculiar noise was caused by some of the cement that had loosened its hold.

We recently had in the store a prescription calling for sodium salicylate dissolved in peppermint water. My manager took a graduate from the rack and dissolved the powder in the liquid by stirring with a glass rod. At once a slight amber color was produced, and as he was not favorable to this brand of sodium salicylate, he said, "It must be contaminated with iron." I could not think this to be the case, as it was the product of a well-known house of excellent reputation. I put the prescription up myself in a graduate that I knew was absolutely clean and I obtained a colorless solution. Afterwards I mixed a little tincture chloride of iron with syrup in a graduate, then washed it (as a boy would perhaps ordinarily wash it) by rinsing it four times under the hot-water spigot, and then put up the prescription as in the first place, getting a colored solution.

Moral: (1) Don't be too quick in condemning chemicals made by a well-known house. (2) Be sure your prescription utensils are absolutely clean.

I was recently asked the question by one of my students, Why calomel was not converted into corrosive sublimate in the stomach by the aid of the hydrochloric acid of the gastric juice? As the

question is one of some interest, I also answer it here. In the first place, the percentage of HCl in the gastric juice is small, only 0·2 per cent.; in the second place, the temperature of the stomach is only 100° F.; in the third place, the food does not remain in the stomach subject to the action of the gastric juice more than two or three hours. In the experiment of Rutherford and Vignal 5 grains of calomel were subjected to the action of the normal gastric juice for *seventeen* hours at a temperature of 100° F. and not more than $\frac{1}{35}$ of a grain of corrosive sublimate was produced. What does take place is probably the formation in the stomach of a complex albuminate of mercury, sodium and chlorine, or if it reaches the duodenum unchanged, which probably is the case, it is decomposed and the gray oxide is precipitated.

RECENT LITERATURE RELATING TO PHARMACY.

HORSE-CHESTNUTS AS FOOD.

Dr. Loves, of Hanover, presented at a recent meeting of *German Naturalists and Physicians* a paper on this topic. He said that if the ground seed be macerated in alcohol, the bitter principles are extracted, and the residue, a white, tasteless powder, is of high nutritive value. The analysis of the seed gives 8 per cent. proteid, 7 per cent. fat, 77 per cent. nitrogen-free extract and 2·6 per cent. ash. The nitrogen-free extract contains about 14 per cent. of cane sugar (in the unripe seeds invert-sugar is present) 13 per cent. of glucosides and 0·2 per cent. of tannic acid. The ingredients that pass into the alcohol include certain phenolic bodies and a substance resembling saponin. The process is covered by patent (now being operated), and it is also proposed to utilize the carbohydrates for the production of alcohol. It is said that 25 litres of alcohol can be obtained from 100 kilos of seeds, and that a plantation of trees will yield yearly 400 marks per hectare (about $40 per acre).

HENRY LEFFMANN.

ERRORS IN KJELDAHL PROCESS.

C. A. Mooers, chemist at the Tennessee Experiment Station (*University of Tennessee Record*, May, 1902) gives figures to show that in that form of the Kjeldahl method, in which mercury is used in the digestion, some of the mercury is carried over in the subse-

quent distillation, even if the safety-bulb is used and an amalgam is formed on the block-tin tubes, which causes some of the ammonia to be retained. Mooers' figures show a loss in some cases of over 15 per cent. He found it impracticable to bring the tubes into a satisfactory condition and replaced them with Jena-glass tubes which, after a year's use, have shown excellent results. He regards these glass tubes as cheaper and better than block-tin. Block-tin tubes can be used safely with the Gunning modification.

Mooers also finds a source of error in following the official A.O.A.C. method for nitrates. He advises that the sample of fertilizer, in which nitrates are to be determined, should be mixed with 1 or 2 c.c. of water, and the mixed acids (sulphuric and salicylic) not added until ten minutes later. H. L.

ASSAY OF COMMERCIAL PEPSINS.

A new method for the assay of commercial pepsins was given in the October "Bulletin of the Pathological and Bacteriological Laboratory of the Delaware State Board of Health." It is essentially the U.S.P. method, excepting that the acid albumen produced by the hydrochloric acid in the pepsin mixture is precipitated by making slightly alkaline with sodium carbonate, leaving only the digested substances, albumoses and peptone in solution.

The number of parts of egg albumen, which 1 part of the pepsin will convert into albumoses and peptone, is ascertained by comparing the nitrogen determination of prepared egg albumen with the digested product by the Kjeldahl method. The author's reason for using this method is that he does not consider a freshly coagulated and granulated egg albumen U.S.P. digested, when it is dissolved, but only when it is converted into those products which are absorbed into the system without further change, namely: albumoses and peptone, products of proteolytic action and not acid albumens. He further states that there is nothing uniform about the strengths of pepsins, either from different firms or the same firm. Appended are a few results obtained by this method of assay upon four of the best-known brands of pepsin, marked 1 : 3000:

Pepsin A	1 : 560
Pepsin B	1 : 1052
Pepsin C	1 : 1209
Pepsin D	1 : 1253

W. S. WEAKLEY.

INTERNATIONAL STANDARD OF POTENT REMEDIES.

Doubtless it would not be practicable to provide in the Pharmacopœia that all tinctures should be prepared with a view to uniformity of dose, desirable as such a provision would be as a means of relieving the practitioner of medicine of the task of remembering a lot of varying doses. Perhaps, however, there might be a nearer approach than has yet been made to a division of tinctures —and of other preparations, for that matter—into classes, the dose of each member of any particular class to be the same. At all events, the various official formularies of the world should show a closer approximation to uniformity in the strength of their preparations than is the case at present. Especially is this desirable in the case of very energetic drugs, in order that overdosing by mistake may be avoided.

A glaring example of the discrepancy in question was made the subject of a paper read at the recent annual meeting of the American Pharmaceutical Association by Mr. M. I. Wilbert, of the German Hospital, Philadelphia. The example pointed out by Mr. Wilbert is that of the United States tincture of aconite, which contains 35 per cent. of the drug, whereas that of France, Hungary and Portugal contains 20 per cent., that of Germany, Austria, Italy, Russia, Roumania, Holland and Switzerland 10 per cent., and that of Great Britain only 5 per cent. The American tincture of this very poisonous drug is, therefore, seven times as strong as the British. It might easily happen, since English medical writings are much read in this country, that an inexperienced American physician should prescribe of our own tincture the dose recommended by an English writer of the British preparation. His patient would then get seven times as much aconite at a dose as the writer relied on had intended. Little is known by the great mass of practitioners in different countries of the discrepancies of the pharmacopœias, and when one finds a certain number of drops of tincture of aconite recommended for a dose, he is very apt not to remember that the tincture which the author had in mind is a very different thing from the tincture that he himself is in the habit of prescribing. There is certainly danger in the existence of such a difference between the aconite tinctures of two nations speaking the same tongue.

But our official formulary is improving in respect to this particular preparation, for when aconite was first made official in the

United States, in 1850, the authorized tincture contained 50 per cent. of the drug, in 1860 the strength was reduced to 40 per cent., and in 1890 it was still further reduced, being made what it is now. That a substantial additional reduction would not prove repugnant to the pharmacists seems probable from Mr. Wilbert's frank remark that "there are probably few pharmacists who would not be willing to double their stock of any preparation by the simple addition of alcohol and water."—*Editorial in N. Y. Medical Journal, 1902.*

OBITUARY.

DR. BRUNO HIRSCH.

Dr. Bruno Hirsch, for many years a corresponding member of this college, and a pharmaceutical writer of international reputation, died at Dresden, Germany, on December 3, 1902.

Dr. Hirsch was born at Görlitz, Germany, on April 13, 1826, where, at the early age of fifteen, he was apprenticed to a local apothecary who with the drug and prescription business combined that of Colonial produce, better known to us as groceries.

It was among such unpromising and, for the scientific development of a meagrely educated youth, uncongenial surroundings that young Hirsch spent the long years of his apprenticeship; this, too, at a time when the duties of an apprentice entailed an amount of drudgery little appreciated by the younger generation, to say nothing of the unduly long hours and the absolute as well as prompt obedience exacted by all the employees older than himself.

It has often been stated that rough words and hard work have never materially injured a superior character, and so in this case, long hours and harsh treatment only proved a stimulus for extra efforts on the part of the apprentice, to demonstrate that he was worthy of something better.

After completing his apprenticeship in Görlitz, young Hirsch went to Berlin, where he acted as assistant in several pharmacies. In 1847 he matriculated at the University of Berlin, and in November of the following year he successfully passed the required State examinations.

His subsequent career as assistant in Berlin, as proprietor of a pharmacy in Grünberg and later in Frankfurt, a. M., was that of a student and careful observer. So that, when ill-health compelled

him to retire from the practice of pharmacy, in 1882, he had at his command an array of experiences and facts that proved the basis of many of his subsequent interesting and valuable contributions to pharmaceutical literature.

From Frankfurt he went to Berlin, but later removed to Dresden so as to be with his only daughter, the wife of Dr. Alfred Schneider.

While the last twenty years of his life formed the period of Hirsch's greatest literary activity, he had for many years been a liberal contributor to the contemporaneous literature of pharmacy, particularly through the pharmaceutical journals of his own country, and as early as 1847 the publication of a critical study, comparing the fifth and sixth editions of the Prussian Pharmacopœias, gave an indication of the natural trend of his studies and observations.

It is along this particular line, the critical, comparative study of the development and contents of the various national pharmacopœias, that Dr. Hirsch has been particularly successful, and in which he was the acknowledged master.

Hirsch published a number of commentary studies relating to the various editions of the Prussian and later the Imperial German Pharmacopœia, and in 1891, in collaboration with his son-in-law, Dr. Schneider, published the first edition of the then Hirsch-Schneider commentary on the third edition of the German Pharmacopœia. This book was immediately and deservedly popular, and has but recently been revised, the third edition being just from the press.

The work that was most congenial to Hirsch, and the one that will no doubt result in the greatest good and the most lasting benefits, is the collation of the Universal Pharmacopöe. The first edition of this work was begun in 1884, and completed three years later, while the second edition, but lately completed, was the last work of this venerable pharmaceutical writer. In the preface to this second edition, dated end of June, 1902, Dr. Hirsch says, "May the last work of a man that has devoted his whole life to the interests of pharmacy, and who is now standing at the close of his life, meet with kindly review and criticisms."

This appeal was hardly needed, as the work referred to is not alone of gigantic proportions, but despite the physical sufferings of the author and the natural infirmities that accompany old age, the amount of collected material, as well as the method, and the gener-

ally acknowledged accuracy of its presentation, will always remain a testimonial to the industry and capacity of this tireless worker.

Some slight idea of the difficulties met with in a work of this kind may be had, when we remember that the twenty-two authoritative books, quoted in the last edition of the Universal Pharmacopöe, required a working knowledge of no less than eleven different languages. The number of separate or distinct titles amounted to 4,450.

That the efforts of Dr. Hirsch to improve the status of pharmacy and to increase the sum-total of our knowledge of drugs and medicines received recognition, is evident from the fact that he was made an honorary member of a number of pharmaceutical societies. Among them the German Pharmaceutical Association, Berlin, the Austrian Society of Apothecaries and our own Philadelphia College of Pharmacy.

Honors of this kind, however, cannot impress the true value of the work done by an individual. Time alone is the test that ultimately determines the real value of any one line of work or investigation. Irrespective of either of these measures of excellence, the published works of Dr. Hirsch are a heritage to us and to succeeding generations, and will, no doubt, prove to be an incentive for better work, in that they demonstrate how, despite adverse surroundings, and hampered by a lack of scientific as well as literary training, it is nevertheless possible to achieve acknowledged scientific standing and to do work of real value for the benefit of our own profession and the general good of the community at large. M. I. W.

PHARMACEUTICAL MEETING.

The regular monthly pharmaceutical meeting of the Philadelphia College of Pharmacy was held Tuesday, December 16th, Mr. W. L. Cliffe, a member of the Board of Trustees, acting as chairman. In calling the meeting to order, the chairman called attention to the importance of the meeting, as the main subject for discussion was one of international importance, and introduced Mr. M. I. Wilbert, who read two papers: one entitled, "International Standards" (see page 13), and the other "The Proposed International Standard Tinctures of Potent Remedies" (see page 20).

Mr. Wilbert exhibited a complete line of tinctures which he had

made from the powdered drugs, these having been supplied by Gilpin, Langdon & Co., according to the proposed international standard.

In discussing the paper, Professor Remington stated that Secretary of State Hay had asked him to suggest the names of two American representatives to "The International Conference for the Unification of Potent Medicaments," and that he had given the names of Dr. H. C. Wood, Philadelphia, and Dr. F. B. Power, now residing in London. Professor Remington also stated that at the Seventh International Congress which met in Chicago, in 1893, the American Pharmaceutical Association appropriated the sum of $1,000 for defraying a portion of the expenses of publishing an International Pharmacopœia of Potent Remedies. He said that this offer was duly presented by him at the Eighth Congress which met at Brussels in 1898, but it was rejected on the ground that the International Pharmacopœia should not be limited to potent remedies but include all remedies. Professor Remington referred to the present work on the revision of the U. S. Pharmacopœia and said that the work was being conducted along lines tending to simplicity and greater uniformity of tinctures as well as other medicaments.

Professor Kraemer read short extracts from a paper communicated by Dr. Power on the recent International Conference (see page 1). Mr. William McIntyre said that he had lived through three or four revisions of the U S. Pharmacopœia and that men do not stop to inquire where new ideas develop, as this does not matter to the patient or druggist so long as they are beneficial. He then referred to tincture of aconite, and said that in his experience there is a tendency among physicians to prescribe it in smaller doses. Mr. McIntyre then offered the following resolutions, which were unanimously adopted:

WHEREAS, It is desirable, if possible, to secure international uniformity in the strength of preparations of potent remedies, therefore, be it

***Resolved*, That we, members of the Philadelphia College of Pharmacy, assembled at this meeting, heartily indorse the spirit of the recommendations of the International Conference for the Unification of Potent Medicaments, held at Brussels, September 15–20, 1902, and be it**

***Resolved*, That copies of this resolution be forwarded to the Chairman of the Committee of Revision of the Pharmacopœia of the United States of America and to the International Secretary for the Unification of the Pharmacopœias.**

Mr. Harry Matusow read a paper on "Hypophosphorous Acid as a Means of Preserving Syrup of Ferrous Iodide." He considered

the various methods which have been suggested to preserve this syrup, and said that so far as he had been able to ascertain, Prof. J. F. Judge, Cincinnati, was the first one to suggest the use of hypophosphorous acid in the preparation of syrup of ferrous iodide, and that it seemed to be the only substance to hold undisputed ground as an effective preservative of this syrup.

Professor Remington said that he did not agree with Mr. Matusow in his statement that the discoloration of the syrup is not due to caramelization of the sugar; he said that this does not always take place at once, and that in nearly all syrups that contain acid, caramelization is likely to take place. Mr. Wilbert said that it was better to make up smaller quantities of preparations of this kind and to make them oftener rather than use preservatives, however harmless they might seem. Mr. McIntyre accorded with this view, and said that personally he had a feeling against using preservatives either for foods or medicine, and that he made his syrups with rock-candy. Mr. Cliffe also advocated the use of rock-candy for the preparation of medicinal syrup. Professor Remington stated that the syrup of iodide of iron would keep better if the amount of sugar were increased about 10 per cent. He also alluded to the late Dr. Charles Rice's method for keeping large quantities of the syrup, and said that he employed a ten-gallon jug with a stop-cock near the bottom for drawing off the syrup, and that it was preserved from the air by the addition of 4 or 5 ounces of olive oil, which formed a layer over the top.

Professor Kraemer spoke of the influence of micro-organisms in changing carbohydrates, and said that in certain instances which he had observed, soluble starch had been changed to the various dextrins and finally glucose in the course of a year through the action of certain fungi, and that in a number of medicinal syrups that had spoiled, the same organisms seemed to be the cause of the spoliation. On the other hand, syrups as well as a large number of other products, including hopped and unhopped wort, which had been properly sterilized and stoppered with absorbent cotton, had been kept for several years.

Mr. Boring stated that he had had some trouble in making a clear preparation of tincture of nux vomica, and that he had found the use of a small quantity of hydrochloric acid to give a clear tincture. Mr. Cliffe said that this might indicate that the trouble was due to

metallic impurities, the acid acting as a solvent for them. Mr. Boring stated that recently he had been preparing this tincture from an extract prepared in vacuo and had not experienced any further trouble. Professor Remington stated that he thought if the precipitate were filtered out it would be found to be inert. He also alluded to the fact that a 20 per cent. aqueous solution of acetic acid would exhaust the whole nux vomica seeds and leave them tasteless. Mr. Boring stated that some years ago Mr. Rother suggested the addition of a small quantity of sodium chloride to the menstruum for exhausting the seeds.

Mr. Wilbert called attention to the special features of the following foreign pharmaceutical books: "Universal Pharmacopöe," by Dr. Bruno Hirsch; "Handkommentar zum Arzneibuch für das Deutsche Reich," by Schneider and Paul; "Anleitung zur Erkennung und Prüfung aller im Arzneibuch für das Deutsche Reich (Vierte Ausgabe) aufgenommenen Arzneimittel," by Dr. Biechle; and "Pharmaceutical Synonyms," reprinted from the *British and Colonial Druggists' Diary.*

PHILADELPHIA COLLEGE OF PHARMACY.

MINUTES OF THE QUARTERLY MEETING.

The quarterly meeting of the members of the Philadelphia College of Pharmacy was held December 29, 1902, in the Library, at 4 o'clock.

In the absence of the President at the opening of the meeting the First Vice-President, William J. Jenks, took the chair. Twenty-one members were present. The minutes of the semi-annual meeting, held September 29th, were read and adopted.

The President, Mr. Howard B. French, having arrived, now took the chair.

The minutes of the Board of Trustees for the regular meetings held September 2d, October 7th and November 5th, and of the special meeting held November 18th, were read by the Registrar and approved.

Professor Lowe suggested extending an invitation to the members of the Third-year Class to attend the special lectures recently established. The President also urged the members to attend and to invite their friends to be present.

Announcement was made of the deaths of Jacob L. Smith (the oldest member of the College in point of membership), T. Morris Perot and George W. Kennedy (active members of the College) and of Dr. Bruno Hirsch, of Dresden, Germany, a corresponding member.

Remarks on the character and services of these gentlemen were made by a number of the members, when, on motion, their names were reported to the Committee on Necrology, to prepare suitable memoirs for publication.

C. A. WEIDEMANN, M.D., *Secretary.*

NOTES AND NEWS.

BENJAMIN HORATIO PAUL, editor of the *Pharmaceutical Journal* for thirty years, has resigned that position. Dr. Paul is not only well known as an editor but also for his labors in pharmaceutical chemistry. A large number of papers of a high order have come from his pen and that of A. J. Cownley, who has been associated with him for more than a quarter of a century. Dr. Paul was recently made an honorary member of the Philadelphia College of Pharmacy in recognition of his splendid services to pharmacy. An interesting sketch of Dr. Paul's career is given in the *Chemist and Druggist*, 1902, pp. 1046 and 1047.

EDGAR F. SMITH, Professor of Chemistry in the University of Pennsylvania and well known for his wide researches in chemistry, has been elected President of the American Philosophical Society, which is distinguished as having been founded by Benjamin Franklin in 1743, and as having a membership including many of the most eminent men in science in this country, and abroad as well.

THE GORDON MEMORIAL COLLEGE at Khartoum, which Lord Kitchener opened on Saturday last, is now ready for the chemical and bacteriological research laboratories presented by Mr. Henry S. Wellcome during his recent visit to the Soudan. The fixtures and appliances made in England have already been shipped, and the equipment for scientific work is, we understand, complete in every detail and will be equal to any similar laboratories in Europe. Dr. Andrew Balfour has been appointed director of the laboratories, and he will find the Soudan to present exceptional opportunities for the study of tropical diseases. Dr. Balfour and his staff will also assist the authorities in forensic investigations, besides giving attention to the study of cereals and textile fibres and to similar matters affecting the development of the agricultural and mineral resources of the country.—*Lancet, November 15, 1902.*

THE DRUG LABORATORY, Bureau of Chemistry, Department of Agriculture, which has been established for the purpose of carrying on work connected with the investigation of drugs, is about ready to begin work, with Lyman F. Kebler as chief chemist. Mr. Kebler is a graduate of the University of Michigan and has received the degrees of B.S. and M.S. from that institution, and has been for some years past chief chemist to the Smith, Kline & French Company, Philadelphia.

"MEEHAN'S MONTHLY," a high-class journal devoted to general gardening and wild flowers, was discontinued with the December issue. This journal was established by the late Thomas Meehan, who was widely known for his original researches in botany, and who aimed in the conduct of this journal to create a love for the beauties of nature and to increase the interest in horticulture and landscape gardening. The publication was eminently successful as an exponent of the science and art of horticulture and general gardening, and it is unfortunate that journals of this character are unable to continue their work without the support of associations or special endowments. It is a matter of great regret that *Meehan's Monthly*, with its proud record, could not longer survive the spirit of its founder.

INTERNATIONAL CONFERENCE FOR THE UNIFICATION OF THE FORMULÆ OF POTENT MEDICAMENTS, BRUSSELS, 1902.

Sterckx Reid Wood Poulsson Greshoff Rost Toth Jorissen Tschirch Jolin Fonck Ranwez Bruylants Möller Heptia.
Buhrer Gusenbourger Heymans Bourquelot Yvon Van Itallie
Naldenovitch Binz Stokvis Mac Alister Schmidt Gariel Devaux Tichomirow Vogl Paterno Codina Depaire Van Hulst Power